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Skeletal Maturation and Elongation in Down's Disease (Mongolism)*

THE INTRODUCTION OF new techniques, including mitotic arrest in cell cultures[28, 55], made it possible to count human chromosomes accurately and to recognize many of their morphological features. These features form the basis for the present identification of individual chromosomes, both as members of a group of chromosomes and as specific elements in the human set of chromosomes (karyotype†).[69, 70] Other techniques are being developed that may allow the certain identification of each chromosome. These include autoradiographic studies of DNA replication[32, 89]. These developments have led to a voluminous literature. It is difficult to evaluate the reliability of so many workers, consequently more weight will be given to reports by established leaders in this field.

Abnormal karyotypes are present regularly in several clinical syndromes. It is reasonable to conclude that these chromosomal abnormalities are responsible for the variations from normal body structure and function (abnormalities of the phenotype) that are recognizable clinically. A less likely alternative is that the chromosomal abnormalities are genetically determined variations from normal body structure at the microscopic level.

Since 1959, it has been known that Down's disease (mongolism) is associated with an additional chromosome.[12, 44, 53, 54] This is referred to as chromosome No. 21 although morphologically it cannot be distinguished at present from either chromosome No. 21 or chromosome No. 22. There is no doubt that Down's disease is a single clinical entity. It would be expected that each individual with this disease would have the same additional chromosome; this has been proven by autoradiographic studies of DNA replication[103]. There has been agreement to refer to this condition as trisomy 21. Trisomy of a chromosome that cannot be distinguished morphologically from No. 21, in association with a clinical state different from Down's disease, is referred to as trisomy 22. This has been reported in several clinical conditions but the balance of evidence suggests that trisomy of chromosome No. 22 is not associated regularly with a syndrome.[78]

In some patients with Down's disease, the additional chromosome No. 21 is not a separate entity but is joined to another chromosome.[30, 39, 71, 72] This phenomenon of translocation occurs in about 3 per cent of individuals with Down's disease.[73, 77] It used to be considered that the apparent effects of an additional chromosome No. 21 were the same whether it was translocated or not.[37] There is a loss of the fused short arms in many translocations;[16, 71, 72] it was concluded that trisomy of the long arm of chromosome No. 21, rather than of the whole chromosome, was the essential abnormality of the karyotype in Down's disease. More recently it has been shown[75, 87] that, in comparison with a free trisomic chromosome No. 21, the corresponding translocated chromosome is associated

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† The following are brief definitions of some terms used in the text: *karyotype*—the systematized arrangement of the chromosomes of a cell; *phenotype*—the external form of an organism; *trisomy*—the presence of a third chromosome of one type in a cell that otherwise has two of each type; *translocation*—the shifting of a segment of one chromosome to another chromosome; *centromere*—a part of each chromosome that does not stain with the usual dyes; *inversion*—rotation of a fragment of a chromosome through 180° after which it is replaced in the chromosome from which it came; *pericentric inversion*—inversion of a fragment that includes the centromere.

with increased whole blood serotonin, reduced activity of several blood cell enzymes and increased response to TSH stimulation. Perhaps these differences are due to the loss of the short arm of chromosome No. 21 when this is translocated. Trisomy of the long arm may result also from pericentric inversion of a maternal chromosome No. 21 leading to duplication of the long arm of this chromosome and the presence of Down's disease in the child.[34] There is a lack of data from biochemical studies of such individuals, similar to those made in cases where chromosome No. 21 was translocated. Occasionally, only a small part of chromosome No. 21 is trisomic; there is associated a slight expression of the clinical characteristics of Down's disease.[24, 42, 61]

Trisomy 21 and the clinical features of Down's disease almost invariably appear together although appearances similar to those of Down's disease have been reported with a karyotype of normal appearance.[38] In this case, an additional chromosome No. 21 may have been translocated to a large chromosome where it would be difficult to detect. The best known trisomy in man is that of chromosome No. 21; many associated changes in the phenotype have been recorded in detail. Because this trisomy is common and because many affected individuals survive until they become adult, it allows an excellent opportunity to observe the apparent effects of an additional chromosome No. 21 on skeletal maturation and skeletal elongation.

Skeletal Maturation

Information concerning skeletal maturation in Down's disease is almost limited to the hand-wrist area. It has been stated, however, that the ischiopubic synchondrosis closes earlier than in normal children[15] and some observations have been made on the spheno-occipital synchondrosis. Early, it was suggested[11] that accelerated maturation of the spheno-occipital synchondrosis, leading to its premature fusion, was responsible for the observed shortness of the cranial base in Down's disease. Post-mortem and radiological findings show, however, that osseous union between the basi-sphenoid and the basi-occiput occurs at a normal or delayed age[6, 35, 97] and that union between the sphenoid and ethmoid is also delayed.[9]

In normal children, the skeletal maturity of the hand-wrist area is a reasonably reliable guide to the maturity of the remainder of the skeleton.[2, 48] In the absence of evidence to the contrary, it may be assumed that the hand-wrist area is an equally useful guide to general skeletal maturity in Down's disease.

Three studies of skeletal maturation in the hand-wrist area have been based on comparatively large samples and on satisfactory standards of maturity.[36] Studies of individuals ranging in age from soon after birth to adulthood have been reported by Pozsonyi *et al.*[74] and by Roche.[81] The former was a cross-sectional study of 100 individuals; the latter was a mixed longitudinal study of 149 children. Rarick *et al.*[76] have reported a cross-sectional analysis of data from a mixed longitudinal study of sixty-four children with Down's disease aged seven to sixteen years.

At all ages until adulthood, the mean skeletal ages of children with Down's disease are less than the corresponding chronological ages[76, 81] except in the comparatively few ($N < 15$), aged more than eight years, included among those studied by Pozsonyi and his co-workers.[74] These findings are in general agreement with many earlier reports that have been reviewed elsewhere.[81] They cannot be reconciled with statements that centres of ossification become radiologically visible at normal or early ages[4, 26, 51, 105] and that the skeletal ages are similar to the chronological ages in most children with this disease.[41, 94] The lack of agreement may be due partly to inadequate samples and partly to the large variability of age at onset of ossification[13, 68, 91] and of skeletal maturity in Down's disease.[81]

There is suggestive evidence that trisomy 21 is associated with more marked skeletal retardation in males than females in the data of Menghi[58] and Pozsonyi *et al.*[74] but this is

not substantiated by the data of Roche[81] and Rarick *et al.*[76] The study of additional large samples is necessary to determine this matter.

Mean standard deviation levels of skeletal maturity in Down's disease have been obtained by dividing the difference between the mean chronological and mean skeletal ages by the standard deviations of the mean skeletal ages in normal children.[36] These levels were calculated from the data of Roche[81] for each sex separately and were combined after it had been shown that the sex differences between the means were not statistically significant. At ages less than two years, the rapid changes in mean level may be due to the small sizes of the samples at these ages (Figure 1). The mean level falls, in relation to the normal

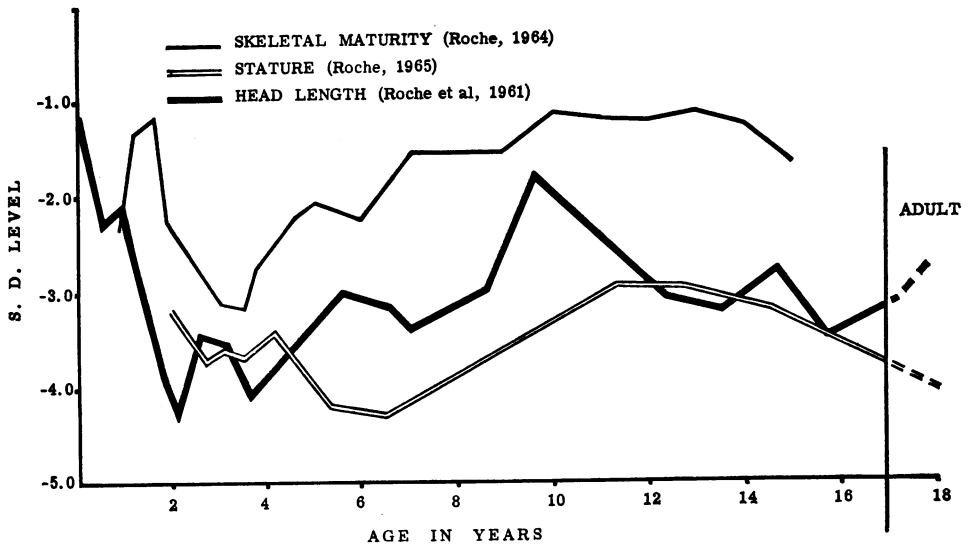

FIGURE 1

Mean standard deviation levels of skeletal maturity, stature and head length in Down's disease.

mean, between the ages of 2 and 3·75 years. At progressively older ages, this level rises until the age of ten years after which further changes are slight.[81] At all chronological ages up to adulthood[74, 81] the mean levels of skeletal maturity are at least 1 s.d. below the normal mean.[36] It is clear that the presence of an additional chromosome No. 21 is associated with a retardation in the mean rate of skeletal maturation both before birth and until the age of about 3·75 years although the mean rate of skeletal maturation is more rapid than normal during the approximate age range 3·75 to 10 years.

The mean rates of skeletal maturation in individual children with Down's disease are slower at chronological ages younger than six years than at older ages ($P < 0{\cdot}01$). In these younger children, the mean rates of skeletal maturation are slower than those of normal children of corresponding age to a statistically significant extent. At older ages, there are no real differences between children with Down's disease and normal children in their mean rates of skeletal maturation.[81] At all chronological ages, the variability of the rates of skeletal maturation is much higher in Down's disease than in normal children.[81] This is consistent with the marked variability of other aspects of this syndrome.[56, 82, 84, 85]

Bullard[14] reported that the carpal and forearm bones were more retarded than the other bones of the hand-wrist area in children with Down's disease. This has not been confirmed in a report by Roche[81] of the mean differences between the skeletal ages of

individual bones and the mean skeletal ages on the same sides of children with Down's disease who were aged about four years. In Figure 2, these mean differences have been adjusted for the corresponding differences in normal children of similar age.[80] As a result, compensation has been made for possible differences in assessment techniques between Roche and the authors of the atlas of standards used, Greulich and Pyle,[36] and also for

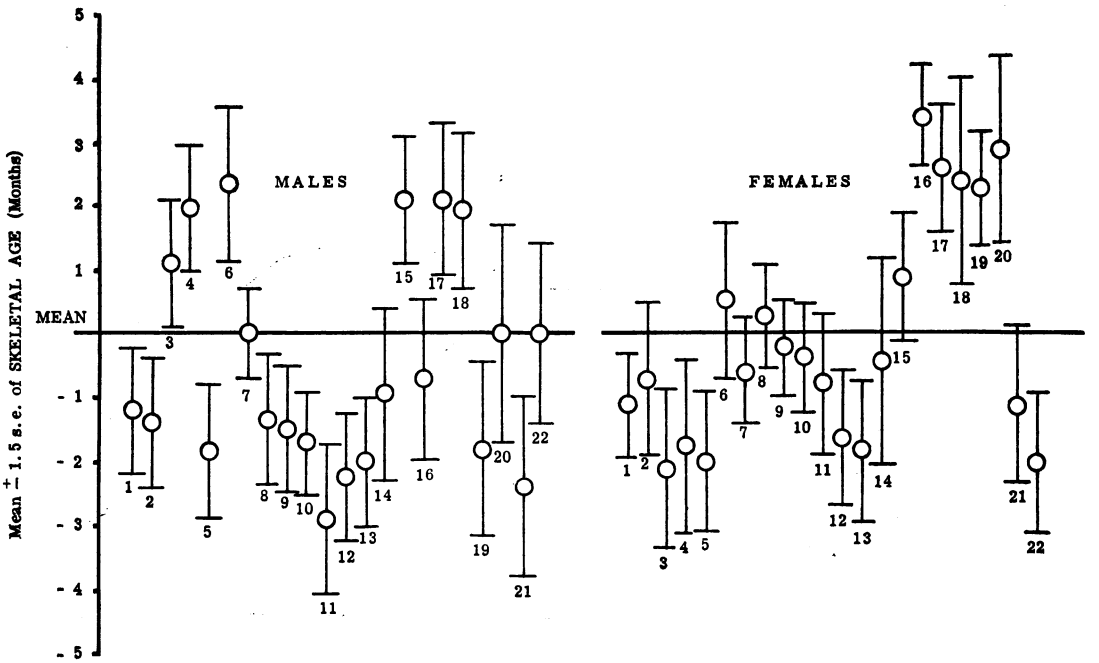

FIGURE 2

The variations of the skeletal ages of individual bones from the mean skeletal ages of the hand-wrist areas on the same sides of the same individuals with Down's disease. These have been corrected for racial and observer variations (see text). Each vertical line represents the mean (0) ± 1·5 s.e. The numbers indicate bones as follows:

1–5 Metacarpals I–V	6–10 Proximal Phalanges I–V	11–14 Middle Phalanges II–V	
15–19 Distal Phalanges I–V	20 Radius	21 Capitate	22 Hamate

possible racial differences between the sample of children with Down's disease studied by Roche[81] and the normal children from whom the standards were derived. Therefore the variations in the mean skeletal maturity of individual bones recorded in Figure 2 are associated with the presence of an additional chromosome No. 21. If, within a sex, the intervals from +1·5 s.e.* to −1·5 s.e. overlap for two bones in Figure 2, the difference between the variations of the mean skeletal ages of these bones from the mean skeletal ages of the hand-wrist areas, on the same sides of the same individuals, is not statistically significant at the 5 per cent level. For example, in the males, the variation of the mean skeletal age of the first metacarpal from the mean skeletal ages of the hand-wrist area on the same sides of the same individuals is significantly different statistically from the corresponding variations of the third and fourth metacarpals, the first proximal phalanx and the first, third and fourth distal phalanges. In each sex, the s.e. of the variations of the means are larger than in normal children.[80, 81]

There is a slight tendency in the females, but not in the males, for individual bones,

* s.e. = standard error.

among the metacarpals and rows of phalanges, to be progressively less mature as they are closer to the ulnar side of the hand (Figure 2). There are wide differences between males and females with Down's disease, and between children with Down's disease and normal children, in the tendencies of particular bones to vary in maturity from the mean skeletal age of the hand-wrist area on the same sides of the same individuals.[80, 81] Some of these differences could be due to sampling. In both normal children and in children with Down's disease, the mean skeletal age of the fifth middle phalanx is retarded relative to the mean skeletal age of the hand-wrist area on the same side. This may be associated with its hypoplasia; this is more common in children with Down's disease than in normal children [79]

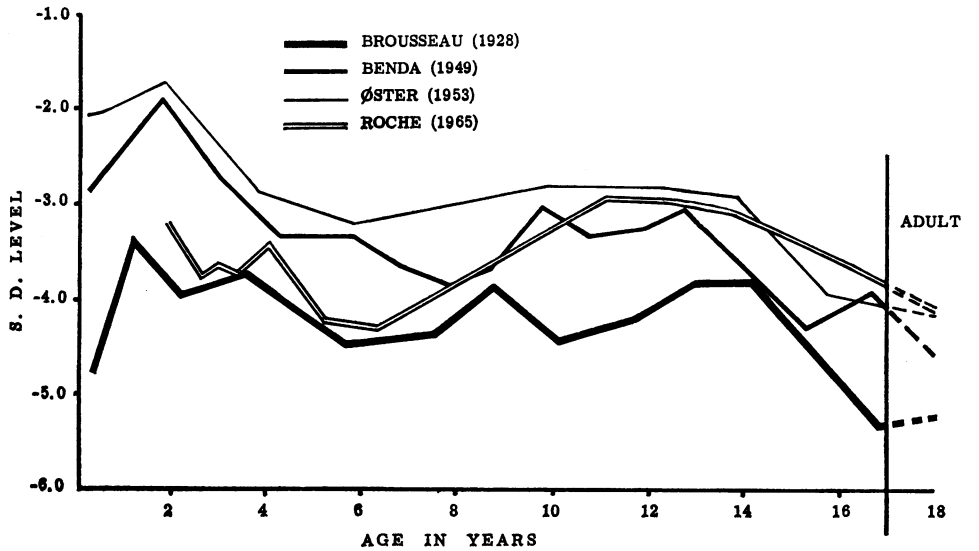

FIGURE 3

Mean standard deviation levels for stature in Down's disease.

Stature

Most data concerning skeletal elongation in Down's disease are derived from observations of stature. Many have reported a shortness of stature but few have based their accounts on sufficiently large amounts of relevant data supported by adequate statistical analyses. Comparison between cross-sectional data derived from four large samples[7, 13, 82, 105] has been simplified by calculating standard deviation levels using corresponding means and standard deviations for normal children.[1] In each of these four studies, the differences between the mean levels in the two sexes were not significant statistically, although it has been claimed that the retardation of stature in this disease is more marked in females than in males.[60] Subsequently data from the two sexes were combined with suitable weighting.

The patterns of change with age in the mean standard deviation levels derived from these four studies[7, 13, 82, 105] show a considerable measure of agreement (Figure 3). The mean levels are below normal at all ages. They rise between birth and the age of two years and then fall until about the age of six years. After the latter age, there are rises until about the age of ten years and the levels then vary only slightly until about the age of twelve years when falls begin that continue into adulthood. Each rise in these mean levels provides evidence of an age range during which the mean statures of children with Down's disease increase more rapidly than those of normal children. It is clear that trisomy 21 is associated with a slow rate of skeletal elongation during the prenatal period, although the mean rate

is more rapid than that for normal children during the first two years of postnatal life and during the age range six to ten years.

To understand the biology of Down's disease, it is important to note that periods occur during which the mean rates of skeletal elongation are more rapid than in normal children although the mean statures of children with Down's disease are markedly less than those of normal children at all ages. The evidence on which these conclusions are based, supported by those of Gustavson,[37] disprove the claims of Siegert,[91] Talbot,[98] Benda[4] that in Down's disease the total body length is normal at birth and that the increase in length is normal during the first year of postnatal life.

The mean levels derived from the data of Benda[7] and Øster[105] are similar but, at most ages, are higher than those derived from the data of Brousseau[13] and Roche[82]. This might be due in part to the use of the same data from normal children[1] to obtain standard deviation levels for each sample. In addition, these differences might reflect variations in the standards of institutional care, in the incidence of other diseases and in the selection of the samples studied. Rickets may be the most important of the associated diseases; for example, each of the twenty-five children with Down's disease reported by Wile and Orgel[102] also had rickets. Those examined by Roche[82] were not a random sample; they were sufficiently co-operative to allow anthropometric and radiographic examinations. This selection may have included more of those who approached normal levels for stature and fewer of those who were markedly below normal levels.[4, 21, 59] It is probable that similar considerations apply to the selection of those studied by some others although Kisling[49] obtained satisfactory records of almost all he attempted to examine.

Among children with Down's disease, of the same sex and of similar age, stature is more variable than in normal children.[82] Correspondingly, serial records of growth in stature in such children show marked variations.[82] In some of these children secondary sexual characters develop without a pubescent spurt in skeletal elongation,[82] although these phenomena are associated closely in normal children.[65] In the majority of children with Down's disease, there are pubescent spurts of growth in stature over a wide spread of ages the mean of which does not differ markedly from normal.[82]

The retardation of skeletal maturation, in association with trisomy 21, would lead one to expect that these children would reach their adult statures at later ages than do normal children. Actually, in Down's disease the mean age at which increase in stature ceases in each sex is younger than that in normal children[19] to an extent that is highly significant statistically.[82] In Down's disease, skeletal elongation ceases at levels of skeletal maturity when there are considerable potentials for increase in stature in normal children.[3] In normal children, skeletal elongation ceases before the final phase of skeletal maturation,[66] but in children with Down's disease these two processes are separated at much earlier than normal chronological and skeletal ages.

Published data from children with Down's disease allow mean standard deviation levels for skeletal maturity to be compared with corresponding levels for stature derived from substantially the same group of children.[81, 82] The mean levels for stature (Figure 1) are considerably lower than those for skeletal maturity at all ages. There are similar patterns of change with age in these two mean levels, but those of skeletal maturity occur about two years earlier than those of stature.

These variations with age in the mean standard deviation levels of skeletal maturity and stature, and the dissociation between maturation and elongation in the latter phase of adolescence,[82] indicate that, at particular skeletal ages, the percentages of mature stature achieved by children with Down's disease would differ from those achieved by normal children. The contrary opinion of Dutton[25] is based on the unacceptable assumption that all children with Down's disease will have the same stature at maturity as the mean for adults with this condition.

Elongation of Bones and Skeletal Areas

Little is known of the elongation of particular bones and skeletal areas in children with Down's disease although such studies could yield valuable information concerning the variations between the apparent effects of an additional chromosome No. 21 on different parts of the skeleton. Such information could assist an understanding of the genetic basis of individual differences in skeletal growth.

Head length is correlated highly with the length of the cranial base.[92] The mechanisms of elongation in the cranial base[29] are similar to those at the epiphyseal regions of long bones[100] where the changes occur that are responsible for the elongation of these bones and, consequently, for the greater part of increase in stature. In normal children, there is a positive correlation between the rate of maturation of the spheno-occipital synchondrosis and that of the hand-wrist area.[50] It may be conjectured that similar correlations exist between the maturation of the other sites of elongation in the cranial base and the maturation of the remainder of the skeleton in normal children and that the rates of maturation and elongation are correlated closely in the cranial base, as in the epiphyseal regions.[3]

It is of some interest, therefore, to compare the mean standard deviation levels of head length and of stature in children with Down's disease. The claim that head length and stature are reduced below normal to similar extents in these children[27] is confirmed by an analysis of more recent data.[82, 86] (Figure 1). Mean standard deviation levels of head length and of stature are below normal to similar extents during the age ranges 2–4·5 years and 12–16 years, but the mean levels of head length are higher than those of stature at other ages. The fluctuations with age in the mean levels of the two measurements are approximately parallel but those of stature occur about two years later than those of head length.

It would have been preferable to have compared directly the rates of elongation of the cranial base and of growth in stature but data relevant to the cranial base that are suitable for such an analysis are not available. In children and in adults with Down's disease, the length of the cranial base is less than normal;[31, 35, 57a] much of this shortening is in the anterior cranial fossa.[9, 49, 57a] Early workers reported that the fused basi-sphenoid and basi-occiput was normal in length[31, 35] but others have claimed that the body of the sphenoid,[4, 9] the basi-sphenoid[4, 35, 57a] and the basi-occiput[9, 43] are short. In the mongoloids aged less than 3·1 years studied by McSweeney[57a] the length of the basi-occiput was normal. There is histological evidence of a slow rate of elongation at the spheno-occipital synchondrosis[5, 6, 9, 26, 52] and a thorough cephalometric study of a large sample by Kisling[49] has shown that the combined basi-sphenoid and basi-occiput is short in adult males to a statistically significant extent. This shortening is relatively less than that of stature. The data from adult males reported by Kisling[49] show a mean level for stature of −3·5 s.d. but a mean level for the combined length of the basi-sphenoid and basi-occiput (S-Ba) of −1·8 s.d. in the same individuals.

In Down's disease the mandible elongates more slowly than normal.[33, 35, 49, 93] It has been described as prognathous,[13, 45, 88, 96, 101] but, in the majority this appearance is due to a tongue thrust.[33]

Evidence relating to the length of the vertebral column in children with Down's disease is derived from measurements of sitting stature. It has been claimed that this is normal until about the age of five years[98] but that it is below the mean at later ages.[102] The ratio $\frac{\text{sitting height}}{\text{stature}}$ is high[13, 22, 31, 99] indicating that the rate of elongation of the vertebral column is closer to normal than that of the lower extremities. Sitting height is an unsatisfactory measurement because it is influenced by the thickness of the soft tissues of the buttocks and by the degree of contraction of gluteal muscles. Furthermore, the measurement

includes the intervertebral discs. Consequently, changes with age in this measurement are difficult to interpret.

The lengths of the lower extremities are below normal at all ages,[13, 46, 98] but it has been stated that this shortness is less marked at the age of seven than at thirteen years.[23] This may be related to the rise in the mean standard deviation level of stature that occurs at about the same age (Figure 3). Several have claimed that the shortness of bones in the lower extremities of children with Down's disease is more marked in the distal portions[9, 20, 63, 98, 105] but there is evidence that the length of the femur is more markedly below normal than that of the tibia.[23, 31]

In Down's disease, the upper extremity is shorter than normal;[23, 98, 105] this shortness is more marked than that of stature.[22, 23, 105] It has been stated that the more distal parts of the limb are particularly short[9, 13, 20, 23, 97] but few have stated the factual basis for their claims. There is evidence that the hand is not relatively shorter than the remainder of the limb[105] and that there is no proximo-distal gradient of shortening within the hand.[41] Both in the lower and the upper extremity, the many claims that shortness is more marked in the distally placed bones must be regarded as unproven. It is a suitable subject for research. The fifth middle phalanx of the hand is short in many individuals with Down's disease; this occurs much less commonly in normal children also.[37, 41, 79, 95]

The ratio $\frac{\text{arm span}}{\text{stature}}$ is lower than normal in Down's disease.[22, 23, 62, 104] The significance of an arm span measurement is difficult to interpret because it reflects the transverse diameter of the thorax and the length of each upper extremity. Furthermore, it is difficult to measure arm span satisfactorily even in a fully co-operative individual although the method described by Davenport[22] should produce reliable results.

Histological studies have shown that the rate of elongation at the anterior ends of the ribs is depressed.[6, 52] The relative chest circumference is approximately normal;[22, 98, 102] consequently the depression of elongation at the anterior ends of the ribs must be similar in degree to that of elongation in the skeleton generally.

The height of the cranium is not strictly relevant to skeletal elongation but it may be considered as a component of stature. At all ages, the mean cranial heights of individuals with Down's disease are markedly below normal[83] but there are wide variations between the mean standard deviation levels derived from data reported by different workers.[47, 62, 90]

In some individuals, the additional chromosome No. 21 is present in some cells but the other cells have a normal karyotype. Usually these children are referred to as mosaic mongoloids and their phenotypes vary widely. Some are typical victims of Down's disease,[10, 77] others approach normality[17, 18] but most have a phenotype that is intermediate between that of a normal individual and that of Down's disease.[40, 57, 64, 67] Few reports of children with a mosaic form of this disease contain information concerning the maturation and elongation of the skeleton. Those that are available[17, 18, 57] indicate that wide variations occur.

It is probable that the large variations between the phenotypes of individuals with mosaic forms of trisomy 21 will not be understood completely until the karyotypes of all varieties of body cells can be identified. At present, there is no definite knowledge of the age-specific and cell-specific critical levels for the incidence of trisomy 21 beyond which abnormalities occur in the phenotype. In addition, the tissues used for cell culture may not be representative of the whole body and the proportions of cell types found in these cultures may not be the same as those in the intact tissue. Even in an individual, there may be changes with age in the proportions of cell types due to selective proliferation of the normal cells. At present, mosaicism can be demonstrated only if the different cell types proliferate in the culture.

Conclusion

This review has drawn attention to several little-known facts concerning Down's disease. These include the variability of the clinical picture, not all of which is associated with recognizable variations in chromosomes. In this disease there are periods when the mean rates of skeletal maturation and skeletal elongation are more rapid than those of normal children. Furthermore, children with Down's disease may reach puberty without a preceding increase in the rate of skeletal elongation. In adolescence, there is a dissociation of skeletal maturation from skeletal elongation at younger than normal ages, after which skeletal maturation proceeds without further skeletal elongation. Presumably, these features of the disease reflect age-specific effects of the additional chromosome No. 21. It does not appear that there are any sex-specific effects of this additional chromosome.

If it is accepted that the presence of an additional chromosome No. 21 is responsible for the abnormalities that are recognizable clinically as Down's disease, two major research challenges become apparent. First, to prevent trisomy 21, and secondly, to prevent the deleterious effects of this additional chromosome on many types of body cells. Neither of these aims is impossible.

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